Nature Reviews Gastroenterology & Hepatology | Published online 13 Dec 2017; doi:10.1038/nrgastro.2017.175

BILIARY TRACT

MMP7 — a diagnostic biomarker for biliary atresia

Serum levels of matrix metalloproteinase 7 (MMP7, also known as matrilysin), combined with γ-glutamyltransferase (GGT) concentration, is an accurate diagnostic biomarker for biliary atresia, reports a new study published in *Science Translational Medicine*. Mechanistic experiments also reveal a role for MMP7 in mediating biliary injury in the disease.

Biliary atresia is a rare, progressive cholangiopathy that affects infants, in which fibrosing injury to extrahepatic bile ducts (EHBDs) in response to an unknown insult leads to cholestasis and jaundice. Despite a low incidence, biliary atresia represents the most frequent indication for liver transplantation in childhood. The aetiology of the condition remains unclear, and emerging evidence has suggested a number of causative factors, including viruses, genetic susceptibility or environmental agents. Early identification of the condition is crucial for good outcomes. However, the current best-performing circulating biomarkers (such as GGT levels) have low sensitivities or no prospective validation, making the identification of minimally invasive, highly discriminatory analytes an urgent unmet clinical need.

To identify potential biomarkers for biliary atresia, Chatmanee Lertudomphonwanit and colleagues used proteomics to screen serum samples obtained from 35 infants at the time of biliary atresia diagnosis and 35 infants diagnosed with intrahepatic cholestasis. Seventy-six proteins were differentially expressed between the two groups; in multivariable logistic regression, the combination of serum levels of MMP7 and GGT differentiated between the two diseases with an area under the receiver operating characteristic curve (AUROC) of 0.98, outperforming all other individual proteins or serum markers. This high performance was maintained in a separate validation cohort ($n = 35$ for each condition) with an AUROC of 0.94. On the basis of these data, the researchers estimated that 19.1 infants could be diagnosed with biliary atresia using the MMP7 plus GGT biomarker before a misdiagnosis would occur.

The researchers next sought to uncover the mechanistic basis for MMP7 as an effective biomarker. Immunohistochemical staining of healthy human liver and biliary tissue revealed MMP7 expression only in EHBD cholangiocytes. Conversely, whole-liver MMP7 expression was increased and intrahepatic cholangiocytes had detectable MMP7 levels in patients with biliary atresia.

Notably, despite the well-known role of MMP7 in extracellular matrix remodelling, serum MMP7 levels were not related to the degree of biliary fibrosis in human tissue samples. However, in a rotavirus-infection model of biliary atresia in mice, which results in EHBD cholangiocyte injury, serum MMP7 levels were markedly increased. Furthermore, inhibition of MMP7, but not other MMPs, in the same model reduced liver injury, prevented EHBD injury and obstruction, and reduced expression of inflammatory markers. On the basis of these findings, the authors propose a role for MMP7 in the pathogenesis of biliary atresia, and suggest that it might represent a target for therapeutics.

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ORIGINAL ARTICLE Lertudomphonwanit, C. *et al.* Large-scale proteomics identifies MMP-7 as a sentinel of epithelial injury and of biliary atresia. *Sci. Transl Med.* **9**, eaan8462 (2017)